However solely to advance prosecution with the Office, Applicant has amended claim 13 along lines suggested by the Examiner ie., the recited derivative of the recombinant human neutral sphingomyelinase now has at least about 70% identity to the protein of SEQ ID NO. 2. Accordingly, claim 13 now features more particular derivatives of the human neutral sphinogmyelinase (N-SMAse) enzyme as represented by SEQ ID NO.2.

Such preferred derivatives of N-SMAse find ample support throughout the specification as filed originally. See Applicant's specification at pg. 9, lines 16-20, for instance.

In view thereof, reconsideration and withdrawal of the rejection under 35 USC §112, first paragraph, are respectfully requested.

Claims 13-17 and 31 stand rejected under 35 USC §103 as being unpatentable over Chatterjee et al. (JBC (1989) 264: 12554); Ogita et al. (WO 95/18119); and Ausubel et al. (Current Protocols in Molecular Biology). Applicants respectfully traverse the rejection.

As understood, the USPTO maintains the position that it would be obvious to make the recombinant N-Smase enzyme of claim 1 by isolating the cited natural N-Smase enzyme, using that enzyme to obtain protein sequence and employing Ausubel's teachings to take that sequence, make cDNA, and then use that to obtain the recombinant N-Smase enzyme. However for reasons already mentioned in the prior response, it is believed that the Office has failed to make a *prima facie* case.

For instance, no prior protein or nucleic acid sequence has been cited by the USPTO and knowledge of Ausubel's general cloning methods, without more, is not sufficient to render the claimed invention obvious.

Applicant's position is compelling in view of the Declaration of Dr. Subroto Chatterjee (dated November 12, 2002) in which he stated, among other things, that the USPTO position was

not tenable with respect to the isolation of this particular enzyme. Specifically, he stated that it was not possible to make the recombinant N-Smase enzyme of claim 1 by using the approach outlined by the USPTO. Specifically, Dr. Chatterjee stated that it was not possible to obtain peptide sequence from the cited N-Smase enzyme and then use that sequence to make cloning probes. Declaration at ¶ 6-8.

However, and as stated by Dr. Chatterjee at ¶ 9-10 of the Declaration, he was able to make the recombinant N-Smase enzyme by using a protein expression cloning method. Use of that method according to Dr. Chatterjee required the isolation of a new antibody that was not taught or suggested from any of the cited references.

In the face of such compelling evidence that the recombinant N-Smase enzyme was indeed difficult to isolate and certainly not obvious from the cited references, the USPTO simply dismissed the evidence on grounds that Applicant should have been able to overcome his problems. Action at pgs. 9-10, bridging paragraph. Respectfully, that is no basis for maintaining the instant rejection because it ignores actual technical difficulties Applicant and skilled colleagues (from Harvard University) faced when they attempted to isolate the recombinant enzyme. Declaration at ¶6-8. None of these difficulties or a solution to them is taught or suggested by the references as relied on.

Applicant notes that one alternative isolation method proposed by the Office at pg. 10 of the Action (expression cloning) would require use of an antibody that recognizes the N-Smase enzyme. None of the cited references provides any specific teaching or suggestion about how to obtain or make such an antibody. Not surprisingly, the instant Office Action is silent as to where this antibody is to come from or whether a suitable antibody could be made at all. Indeed, it was the Applicant who discovered that it was possible to make a monospecific antibody against N-Smase and that the antibody could be used to isolate the recombinant enzyme. Declaration at ¶ 9-14.

In view thereof, reconsideration and withdrawal of the obviousness rejection are respectfully requested.

Applicant disagrees with the rejection on additional grounds.

On pages 11-12 of the instant Action, the Examiner indicated that the obviousness rejection may be reconsidered if Applicant shows that the recombinant enzyme had unique properties which the natural enzyme of Chatterjee et al. does not. Although Applicants do not believe that such information is needed to address the instant rejection, it is provided below to help further prosecution.

As an initial matter, Applicant respectfully requests consideration of the attached Supplemental Declaration of Dr. Subroto Chatterjee (unsigned). Consideration of the Declaration at this time is earnestly requested in light of the Examiner's request for additional enzyme information in the instant Office Action. A signed Declaration will follow under separate cover.

In the Supplemental Declaration, Dr. Chatterjee states, among other things, that he had problems using the natural enzyme in the claimed method. Declaration at ¶ 6. In particular, he states that the **natural enzyme had tightly associated proteases and phosphatases**. These unwanted proteins resist purification, degrade the natural enzyme, and render it unsuitable for use in the claimed method. Unlike the natural enzyme, the recombinant N-Smase was not found to be associated with any detectable protease or phosphatase activity. Declaration at ¶ 7.

Dr. Chatterjee also states in the Supplemental Declaration that the **recombinant N-Smase enzyme was more stable then the natural enzyme**. Declaration at ¶ 8. Specifically, he states that the recombinant enzyme was more stable then the natural enzyme which resulted in better assay sensitivity and reproducibility. Declaration at ¶ 8.

As also stated in the Supplemental Declaration at ¶ 9, **storage of the natural N-Smase produced unwanted proteolytically digested products**. According to Dr. Chatterjee, such products can contribute to false or misleading identification of compounds in the claimed method. In contrast, storage of the recombinant N-Smase did not result in production of detectable digestion products. Declaration at ¶ 9.

Accordingly, the natural N-Smase enzyme cited by the Office has characteristics that are different from the recombinant enzyme of claim 1. For instance, and as the Supplemental Declaration makes clear, the recombinant enzyme does not have any detectable protease and phosphatase activity. In contrast, the natural enzyme has these damaging enzymes tightly associated with it. Moreover, the recombinant enzyme is more stable and less prone to proteolytic digestion when compared to the natural N-Smase enzyme. These and other advantages of the recombinant N-Smase enzyme make it especially useful for use in the claimed invention.

None of the cited references cited by the Office teach or suggest the foregoing problems associated with using the naturally-occurring N-Smase in accord with the claimed invention. Moreover, none of the cited references disclose or suggest Applicant's solution to these problems ie., making the recombinant N-Smase and using that enzyme instead of the natural enzyme in the claimed method.

Accordingly, and in view of reasons already of record, reconsideration and withdrawal of the outstanding obviousness rejection are respectfully requested.

If for any reason a fee is required, a fee paid is inadequate or credit is owed for any excess fee paid, you are hereby authorized and requested to charge Deposit Account No. **04-1105**.

Respectfully submitted,

Date: 27 May 03

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 13 was amended as follows:

13. (Amended) A method [of] for identifying a compound useful in the diagnosis or treatment of a human neutral sphingomyelinase related disorder, the method comprising contacting a candidate pharmacological agent with a recombinant human neutral sphingomyelinase having an amino acid sequence represented by SEQ ID NO. 2 or fragment or derivative thereof and analyzing the mixture of the candidate agent and human neutral sphingomyelinase or fragment or derivative thereof, wherein the analyzing step further comprises comparing enzyme activity in the presence and absence of the agent, wherein the fragment or derivative of the human neutral sphingomyelinase has at least about 50% of the activity of the protein of SEQ ID NO.2, wherein the fragment or derivative of the recombinant human neutral sphingomyelinase is at least about 70% identical to the protein of SEQ ID NO. 2.

Claim 31 was canceled without prejudice.

Docket No. 46906-DIV2 (71699)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT:	S. Chatterjee		
SERIAL NO.:	09/282,879	EXAMINER:	M. Rao
FILED:	March 31, 1999	GROUP:	1652
FOR:	RECOMBINANT N-SMASEs AND NUCLEIC ACIDS ENCODING SAME		

THE HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS
WASHINGTON, DC 20231

SIR:

SUPPLEMENTAL DECLARATION PURSUANT TO 37 CFR 1.132

The undersigned declares as follows:

1. I am the inventor of the above-identified application (hereafter the "subject application"). Additionally, I am a Professor of Pediatrics in the Department of Pediatrics at the Johns Hopkins University Medical School in Baltimore, MD.

2. As I understand it, the subject application discloses and claims, among other things, a method of identifying a compound useful in the diagnosis or treatment of a human neutral sphingomyelinase (N-Smase) related disorder. A particular method includes contacting an agent with a recombinant N-Smase and analyzing enzyme activity in the presence and absence of the agent.

3. I have reviewed the Patent Office Action ("Office Action") dated November 27, 2002 issued in connection with the subject application. As I understand the Office Action, the patent Examiner rejected claims 13-17 and 31 as being obvious over Chatterjee et al. (*J. Biol. Chem.* (1989) 264: 12554); Ogita et al. (WO 95/18119); and Ausbel et al. (*Current Protocols in Molecular Biology*, J. Wiley & Sons (1987) pp. 10.0.3

–10.06). Hereinafter, the cited references are referred to as "Chatterjee", "Ogita" and "Ausbel", respectively.

4. I am familiar with the contents of Chatterjee and Ausbel and I have read an English language translation of Ogita. As I understand it, Chatterjee reports isolation of naturally-occurring N-Smase from human urine, Ogita (as translated) reports isolation of a bacterial sphingomyelinase inhibitor from grass, and Ausbel discloses standard cloning methods.

5. I must respectfully disagree with the patent Examiner's position that the method I now claim is obvious over Chatterjee, Ogita and Ausbel. More specifically, I must disagree with the suggestion by the Examiner that it would be obvious to make the recombinant N-Smase featured in the claimed method.

6. For example, I have encountered substantial problems using the naturally-occurring N-Smase of Chatterjee et al. with the claimed method.

7. In particular, I found that even when the natural N-Smase enzyme is highly purified, it includes tightly associated proteases and phosphatases. Unfortunately, these enzymes degrade the enzyme. That activity renders the natural enzyme unsuitable for use with the claimed method. In contrast, the recombinant N-Smase of claim 1 is not associated with any detectable protease or phosphatase activity.

8. I also found that storage of the natural N-Smase enzyme, particularly long term, lowers its specific activity for substrate. This makes that natural enzyme unsuitable for use with the claimed method. Unlike that enzyme, the recombinant N-Smase of claim 1 is more stable. Use of the recombinant enzyme in the claimed method results in better sensitivity and reproducibility, for example.

9. In addition, storage of the natural N-Smase enzyme produces multiple proteolytically digested products. These products are not desirable for use with the claimed method. For example, one or more of the products can contribute to false or misleading identification of compounds according to the claimed method. In marked contrast, I have found that storage of the recombinant N-Smase of claim 1 does not result in detectable production of the digestion products.

10. As I understand the Chatterjee, Ogita and Ausbel references as cited by the Examiner, none of them disclose or suggest the foregoing problems of using the natural N-Smase enzyme with the claimed method.

11. I hereby further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: _____ _____

Subroto Chatterjee